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APPLICANT: Mary Jeanne Kreek et al.

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FOR: **ALLELES OF THE HUMAN ORPHANIN FQ/NOCICEPTIN RECEPTOR GENE, DIAGNOSTIC METHODS USING SAID ALLELES, AND METHODS OF TREATMENT BASED THEREON**

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David A. Jackson, Reg. No. 26,742
(Name of Registered Rep.)

Anne M. Jones 10/9/01
(Signature and Date)

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON DC 20231

Dear Sir:

Prior to calculating claim fees, please enter the following amendments into the file of the present application.

IN THE CLAIMS:

Please cancel claims 1-30 of the present application, without prejudice, and add the following new claims 31-61.

31. A variant allele of a human orphanin FQ/nociceptin receptor gene, comprising a DNA sequence having at least one variation in SEQ ID NO:1, wherein said variation comprises G-46A, GIVS I 135C, GIVS I 250A, GIVS I 251A, C510T, CIVS III 67T, A804G, C1026T, C1126G, or any combination thereof.

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32. The variant allele of claim 31 wherein said allele is isolated.

33. The isolated variant allele of Claim 32, detectably labeled.

34. The isolated variant allele of Claim 32, wherein said detectable label comprises a radioactive element, a chemical which fluoresces, or an enzyme.

35. An isolated nucleic acid molecule selectively hybridizable to the isolated variant allele of Claim 31.

36. The isolated nucleic acid molecule of Claim 35, detectably labeled.

37. The isolated nucleic acid molecule of Claim 36, wherein said detectable label comprises a radioactive element, a chemical that fluoresces, or an enzyme.

38. A cloning vector comprising an isolated variant allele of a human orphanin FQ/nociceptin receptor gene and an origin of replication, wherein said variant allele comprises a DNA sequence of claim 31.

39. A cloning vector comprising an origin of replication and an isolated nucleic acid molecule selectively hybridizable to an isolated variant allele of a human orphanin FQ/nociceptin receptor gene, wherein said variant allele comprises a DNA sequence of claim 31.

40. The cloning vector of either of Claims 38 or 39, wherein said cloning vector comprises of *E. coli*, bacteriophages, plasmids, or pUC plasmid derivatives.

41. The cloning vector of Claim 40, wherein bacteriophages further comprise lambda derivatives, plasmids further comprise pBR322 derivatives, and pUC plasmid derivatives further comprise pGEX vectors, or pmal-c, pFLAG.

42. An expression vector comprising an isolated variant allele of a human orphanin FQ/nociceptin receptor gene comprising a DNA sequence of claim 31.

43. An expression vector comprising an isolated nucleic acid molecule selectively hybridizable to an isolated variant allele of a human orphanin FQ/nociceptin receptor gene, wherein said isolated nucleic acid molecule is operatively associated with a promoter, and said variant allele comprises a DNA sequence of claim 31.

44. The expression vector of either of Claims 42 or 43, wherein said promoter comprises immediate early promoters of hCMV, early promoters of SV40, early promoters of adenovirus, early promoters of vaccinia, early promoters of polyoma, late promoters of SV40, late promoters of adenovirus, late promoters of vaccinia, late promoters of polyoma, the *lac* the *trp* system, the *TAC* system, the *TRC* system, the major operator and promoter regions of phage lambda, control regions of fd coat protein, 3-phosphoglycerate kinase promoter, acid phosphatase promoter, or promoters of yeast α mating factor.

45. A unicellular host transformed or transfected with an expression vector comprising an isolated

variant allele of a human orphanin FQ/nociceptin receptor gene operatively associated with a promoter, wherein said variant allele comprises a DNA sequence of claim 31.

46. A unicellular host transformed with an expression vector comprising an isolated nucleic acid molecule selectively hybridizable to an isolated variant allele of a human orphanin FQ/nociceptin receptor gene, wherein said isolated nucleic acid molecule is operatively associated with a promoter, and said variant allele comprises a DNA sequence of claim 31.

47. The unicellular host of either of Claims 45 or 46, wherein said host comprises *E. coli*, Pseudomonas, Bacillus, Streptomyces, yeast, CHO, R1.1, B-W, L-M, COS1, COS7, BSC1, BSC40, BMT10 or Sf9 cells.

48. A method for determining a susceptibility in a subject to at least one physiological response, condition or disease related to the endogenous opioid system, nociception, neurotransmitter release (including dopamine, GABA, noradrenaline, and serotonin), anxiety and stress, learning, memory and cognition, alcohol self-administration, behavioral sensitization to cocaine, drug addiction, opiate withdrawal and tolerance, food intake, immune function, cardiovascular function, renal function, gastrointestinal function, or motor function, comprising the steps of:

a) removing a bodily sample from said subject, wherein said sample comprises a first and second allele comprising a human orphanin FQ/nociceptin receptor gene;

b) determining whether said human orphanin FQ/nociceptin receptor gene of said first allele comprises a DNA sequence of claim 31, such that the presence of said at least one variation in said human orphanin FQ/nociceptin receptor gene of said first allele is expected to be indicative of the subject's susceptibility to at least one said physiological

response, condition or disease relative to the susceptibility to said at least one said physiological response, condition or disease in a standard.

49. The method for determining a susceptibility to at least one addictive disease of Claim 48, further comprising the step of determining whether said human orphanin FQ/nociceptin receptor gene of said second allele comprises a DNA sequence having at least one variation in SEQ ID NO:1, wherein said variation comprises G-46A, GIVS I 135C, GIVS I 250A, GIVS I 251A, C510T, CIVS III 67T, A804G, C1026T, C1126G, or any combination thereof, such that the presence of said at least one variation in said human orphanin FQ/nociceptin receptor gene of said second allele is expected to be indicative of the subject's susceptibility to said at least one physiological response, condition or disease relative to the susceptibility to said at least one physiological response, condition or disease in said standard.

50. The method of either of Claim 48 wherein said at least one addictive disease comprises opioid addiction; cocaine addiction or addiction to other psychostimulants; nicotine addiction; barbituate or sedative hypnotic addiction; anxiolytic addiction; or alcohol addiction.

51. A method for determining a susceptibility to pain in a subject relative to a susceptibility of pain in a standard, wherein the method comprises the steps of:

a) removing a bodily sample from said subject, wherein said sample comprises a first and second allele comprising a human orphanin FQ/nociceptin receptor gene;

b) determining whether said human orphanin FQ/nociceptin receptor gene of said first allele comprises a DNA sequence of claim 31, such that the presence of said at least one variation in said human orphanin FQ/nociceptin receptor gene of said first allele is

expected to be indicative of susceptibility to pain in said subject relative to susceptibility to pain in said standard, wherein said first allele of said standard comprises a human orphanin FQ/nociceptin receptor gene comprising a DNA sequence of SEQ ID NO:1.

52. The methd of Claim 51 for determining a susceptibility to pain in a subject, further comprising the step of determining whether said second allele of said bodily sample comprises a human orphanin FQ/nociceptin receptor gene comprising a DNA sequence having at least one variation in SEQ ID NO:1, wherein said variation comprises G-46A, GIVS I 135C, GIVS I 250A, GIVS I 251A, C510T, CIVS III 67T, A804G, C1026T, C1126G, or any combination thereof, such that the presence of said at least one variation in said second allele is expected to be indicative of susceptibility to pain in said subject relative to susceptibility of pain in said standard, wherein said second allele of said standard comprises a human orphanin FQ/nociceptin receptor gene comprising a DNA sequence of SEQ ID NO:1.

53. A method for determining a therapeutically effective amount of pain reliever to administer to a subject in order to induce analgesia in said subject relative to a therapeutically effective amount of pain reliever to administer to a standard in order to induce analgesia in said standard, wherein the method comprises determining a susceptibility to pain in said subject relative to susceptibility to pain in said standard, wherein susceptibility to pain in said subject is expected to be indicative of said therapeutically effective amount of pain reliever to administer to said subject to induce analgesia in said subject relative to said therapeutically effective amount of pain reliever to administer to said standard to induce analgesia in said standard.

54. The method of Claim 53 for determining a therapeutically effective amount of pain reliever to administer to said subject, wherein determining susceptibility to pain in said subject comprises the steps of:

a) removing a bodily sample from said subject, wherein said sample comprises a first and second allele comprising a human orphanin FQ/nociceptin receptor gene; and

b) determining whether said first allele comprises a human orphanin FQ/nociceptin receptor gene comprising a DNA sequence of claim 31, wherein the presence of said at least one variation in said human orphanin FQ/nociceptin receptor gene of said first allele is expected to be indicative of the subject's susceptibility to pain relative to said to susceptibility of pain in said standard, wherein said first allele of said standard comprises a human orphanin FQ/nociceptin receptor gene comprising a DNA sequence of SEQ ID NO:1, such that said therapeutically effective amount of pain reliever to administer to the subject in order to induce analgesia is related to said susceptibility to pain in said subject relative to susceptibility to pain in said standard.

55. The method of Claim 54, wherein determining susceptibility to pain in said subject relative to susceptibility to pain in said standard further comprises the step of determining whether said second allele of said bodily sample from said subject comprises a human orphanin FQ/nociceptin receptor gene comprising a DNA sequence having at least one variation in SEQ ID NO:1, wherein said at least one variation comprises G-46A, GIVS I 135C, GIVS I 250A, GIVS I 251A, C510T, CIVS III 67T, A804G, C1026T, C1126G, or any combination thereof, such that the presence of said at least one variation in said second allele is expected to be indicative of susceptibility to pain in said subject relative to susceptibility to pain in said standard, wherein said second allele of said standard comprises a human orphanin FQ/nociceptin receptor gene

comprising a DNA sequence of SEQ ID NO:1, and the therapeutically effective amount of pain reliever to administer to said subject to induce analgesia in said subject is related to the presence of said at least one variation in said human orphanin FQ/nociceptin receptor gene of said second allele of said bodily sample from said subject.

56. A method for determining a therapeutically effective amount of therapeutic agent to administer to a subject suffering from at least one addictive disease to treat the at least one addictive disease in said subject relative to a therapeutically effective amount of therapeutic agent to administer to a standard suffering from the at least one addictive disease to treat the at least one addictive disease in said standard, wherein the method comprises the steps of:

a) removing a bodily sample from said subject, wherein said sample comprises a first and second allele comprising a human orphanin FQ/nociceptin receptor gene; and

b) determining whether said first allele comprises a human orphanin FQ/nociceptin receptor gene comprising a DNA sequence of claim 31,

wherein the presence of said at least one variation in said human orphanin FQ/nociceptin receptor gene of said first allele is expected to be indicative of the therapeutically effective amount of said therapeutic agent to administer to the subject to treat said at least one addictive disease in said subject relative to said therapeutically effective amount of said therapeutic agent to administer to said standard to treat said at least one addictive disease in said standard, wherein said first allele of said standard comprises a human orphanin FQ/nociceptin receptor gene comprising a DNA sequence of SEQ ID NO:1.

57. The method of Claim 56 for determining a therapeutically effective amount of therapeutic agent to administer to a subject suffering from said at least one addictive disease to treat said at least

one addictive disease, relative to said therapeutically effective amount of said therapeutic agent administered to said standard suffering from said at least one addictive disease to treat said at least one addictive disease in said standard, further comprising the step of determining whether said second allele of said bodily sample from said subject comprises a human orphanin FQ/nociceptin receptor gene comprising a DNA sequence having at least one variation in SEQ ID NO:1, wherein said variation comprises G-46A, GIVS I 135C, GIVS I 250A, GIVS I 251A, C510T, CIVS III 67T, A804G, C1026T, C1126G, or any combination thereof, such that the presence of said at least one variation in said second allele related to said therapeutically effective amount of said therapeutic agent administered to said subject to treat said at least one addictive disease in said subject relative to said therapeutically effective amount of said therapeutic agent to administer to said standard to treat said at least one addictive disease in said standard, wherein said second allele of said standard comprises a human orphanin FQ/nociceptin receptor gene comprising a DNA sequence of SEQ ID NO:1.

58. The method of either of Claims 56 or 57, wherein said at least one addictive disease comprises opioid addiction; cocaine addiction or addiction to other psychostimulants; nicotine addiction; barbiturate or sedative hypnotic addiction; anxiolytic addiction; or alcohol addiction.

59. A commercial test kit may for determining the presence of at least one variation in a human orphanin FQ/nociceptin receptor gene of an allele in a bodily sample taken from a subject, wherein the commercial test kit comprises:

a) PCR oligonucleotide primers suitable for detection of an allele comprising a human orphanin FQ/nociceptin receptor gene comprising a DNA sequence having at least one variation in SEQ ID NO:1 comprising G-46A, GIVS I 135C, GIVS I 250A, GIVS I

251A, C510T, CIVS III 67T, A804G, C1026T, C1126G, or any combination thereof;

b) other reagents; and

c) directions for use of the kit.

60. A nucleic acid comprising an intron of the human orphanin FQ/nociceptin receptor gene as set forth in SEQ ID No:2.

61. A nucleic acid as set forth in SEQ ID No:2.

Remarks

The new claims presented above which replace the original claims contain no new matter and were provided simply to reduce the number of claims in the application. Examination on the merits is courteously solicited.

Respectfully submitted,

KLAUBER & JACKSON

David A. Jackson
Attorney for Applicants
Reg. No. 26,742

KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack, NJ 07604
Tel: 201-487-5800